PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
ANGELA DALLAS SEBOR
SHERIDAN ROSS P.C.
1560 BROADWAY, SUITE 1200
DENVER, CO 80202-5141

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference 2848-70-PCT	Date of mailing (*day/month/year*) 02 MAY 2008 **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US05/18879	26 May 2005 (26.05.2005)	27 May 2004 (27.05.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC: **C12Q 1/68**(2006.01);**C07H 21/04**(2006.01)
USPC: 435/6;536/24.3

Applicant

REGENTS OF THE UNIVERSITY OF COLORADO

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	18 April 2008 (18.04.2008)	Larry Helms Telephone No. (571) 272-1600

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

Form PCT/ISA/237 (cover sheet) (April 2007)

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
   - ☒ the international application in the language in which it was filed
   - ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material
      - ☐ a sequence listing
      - ☐ table(s) related to the sequence listing

   b. format of material
      - ☐ on paper
      - ☐ in electronic form

   c. time of filing/furnishing
      - ☐ contained in the international application as filed.
      - ☐ filed together with the international application in electronic form.
      - ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO
Inventive step (IS)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO
Industrial applicability (IA)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO

2. Citations and explanations:

Claims 1, 9, 22-24, 33-36, 41, 42, 46, 53, and 60-62 lack novelty under PCT Article 33(2) as being anticipated by Mischel et al. (US PG PUB 2004/0106141).
Mischel et al. teach a method for determining a mammalian glioma tumor likely to respond to an EGFR inhibitor by detecting the expression of PTEN, EGFR, and phosphorylated AKT wherein increased expression of EGFR and phosphorylated AKT identifies a tumor not likely to respond to an EGFR inhibitor. Mischel, et al. teach detection of the expression products by immunohistochemistry using specific antibodies which may be in a kit with a detectable label and an immobilized substrate.

Claims 1, 9-11, 22-24, 33, 34, 41, and 42 lack novelty under PCT Article 33(2) as being anticipated by Bacus et al. (US PG PUB 2004/0132097).
Bacus et al. teach prediction of a cancer patient's response to epidermal growth factor receptor (EGFR) directed therapy by measuring the expression levels of biomarkers including both EGFR and HER2/neu.

Claims 1, 2, 9, 22-24, 33-36, 41, 42, 46, 53, 55, and 60-62 lack novelty under PCT Article 33(2) as being anticipated by Bacus et al. (US PG PUB 2004/0248151). Bacus et al. teach a method of identifying a tumor that responds to HER2 directed therapy by measuring biomarkers including EGFR and phosphorylated AKT. Bacus et al teach detection of EGFR expression using a microarray and nucleotide probe. Bacus et al teach detection of phosphorylated AKT by immunohistochemistry and a specific antibody to phosphorylated AKT. Bacus et al. teach a kit comprising the reagents for detecting the biomarkers.

Claims 1-3, 9-11, 17, 21-24, 33-36, 41, 42, 46-48, 53, 55, and 59-62 lack an inventive step under PCT Article 33(3) as being obvious over Bacus (US PG PUB 2004/0248151) in view of Hirsch et al. (British Journal of Cancer, 2002). Bacus et al. teach a method of identifying a tumor that responds to HER2 directed therapy by measuring biomarkers including EGFR and phosphorylated AKT. Bacus et al teach detection of EGFR expression using a microarray and nucleotide probe. Bacus et al teach detection of phosphorylated AKT by immunohistochemistry and a specific antibody to phosphorylated AKT. Bacus et al. teach a kit comprising the reagents for detecting the biomarkers. Bacus et al do not teach detection of polysomy of HER2/neu using in situ hybridization in lung cancer. This deficiency is made up for in the teachings of Hirsch et al.
Hirsch et al. teach a method for detecting the association between gene copy number and protein expression of HER2/neu in lung carcinoma patients. Hirsch et al. teach fluorescence in situ hybridization (FISH) to detect gene copy number per cell. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have determined the response to therapy by measuring the biomarkers of Bacus et al. and the gene copy number in view of Hirsch et al.
One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have determined the response to therapy by measuring the biomarkers of Bacus et al and the gene copy number in view of Hirsch et al. because Hirsch et al teach that HER2/neu gene amplification and cell surface expression are important factors in breast cancer prognosis and that FISH is a more accurate and reliable method for selecting patients suitable for breast cancer treatment with trastuzumab than protein detection. Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have determined the response to therapy by measuring the biomarkers of Bacus et al and the gene copy number in view of Hirsch et al.

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V.1. Reasoned Statements:
The opinion as to Novelty was positive (Yes)with respect to claims 3-8, 10-21, 25-32, 37-40, 43-45, 47-52, 54, 56-59
The opinion as to Novelty was negative (No) with respect to claims 1, 2, 9, 22-24, 33-36, 41, 42, 46, 53, 55, 60-62
The opinion as to Inventive Step was positive (Yes)with respect to claims 4-8, 12-16, 18-20, 25-32, 37-40, 43-45, 49-52, 54, 56-58
The opinion as to Inventive Step was negative(NO) with respect to claims 1-3, 9-11, 17, 21-24, 33-36, 41, 42, 46-48, 53, 55, 59-62
The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-62
The opinion as to Industrial Applicability was negative(NO) with respect to claims NONE